REMARKS

It is believed that in view of the amendments and remarks herewith, which obviate the remaining rejections of the May 20, 2002 final Office Action, this application is now in condition for allowance. Consideration and entry of this paper is respectfully solicited.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1, 3-5 and 8-11 and 18-33 are pending. Claims 18-33 have been added, without prejudice, without admission, without surrender of subject matter and without any intention of creating any estoppel as to equivalents. Support for the amendments can be found throughout the specification.

No new matter is added.

It is submitted that the claims, as originally presented, and as herewith presented, are patentably distinct over the prior art cited by the Examiner, and that these claims are in full compliance with the requirements of 35 U.S.C. §112. Changes to claims and/or new claims as presented herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, these changes are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel, as the herewith amendments are not narrowing amendments.

II. THE REJECTION UNDER 35 U.S.C. §103 IS OVERCOME

Claims 1, 3-5 and 8-11 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Inoue *et al.* and Maisonpierre *et al.* in view of Kendall *et al.* and Asahara *et al.* The rejection is respectfully traversed.

The Office Action asserts at page 5 that Inoue *et al.* teach that VEGF is involved in the process of atherosclerosis. While they suggest that VEGF "may have some role in the progression of human coronary atherosclerosis", all they actually demonstrate is that VEGF is expressed in atherosclerotic plaques. They do not establish any cause/effect relationship between the presence of VEGF and the occurrence of the plaques. Instead, Inoue discusses two alternative possibilities: 1) that increasing angiogenesis actually causes plaque growth; and 2) that the growing atherosclerotic plaque delivers some signal that causes the development of blood vessels. This dichotomy of possible relationships between the presence of VEGF and the occurrence of plaques prevents one of skill in the art from having an expectation of success in developing a treatment for atherosclerosis

and/or restenosis on the basis of these findings. Thus, there is no evidence that the growing plaque blood vessels cause the plaque growth (and that thereby, by inhibiting the growth of blood vessels, plaque growth would be inhibited). Hence, it would not be obvious that treatment targeted to inhibiting the growth of blood vessels would have any effect on plaque development.

Inoue also showed that macrophages that accumulated in atherosclerotic lesions were positive for VEGF. It should also be pointed out that VEGF is a potent chemoattractant of monocytes/macrophages, and it is well known that macrophages present in the vessel wall critically contribute to the development of atherosclerosis. The presence of VEGF in an atherosclerotic plaque might therefore be causally related to growth of the plaque, but not because of its effects on angiogenesis. Hence, there are multiple reasons why Inoue's teaching bares no relationship to restenosis, and does not even definitively demonstrate that VEGF contributes to atherosclerosis by the increase development of plaque blood vessels.

Further, Kendell *et al.* only show that a VEGF inhibitor can inhibit mitogenesis. It is indeed a significant extrapolation from limited mitogenesis to the reduction or treatment of restenosis or atherosclerosis. In fact, Kendall *et al.* suggest that their invention might be used to treat a variety of diseases and conditions, specifically listing psoriasis, rheumatoid arthritis, hemangiomas, angiofibromas, diabetic retinopathy, neovascular glaucoma and conditions such as tumor vascularization. Nowhere in their disclosure do Kendall *et al.* teach or suggest the use of a VEGF inhibitor to reduce or treat restenosis or atherosclerosis. Further, they do not teach or suggest the combination of a VEGF inhibitor with another molecule generally or an angiopoietin specifically.

Maisonpierre *et al.* report that Ang1 is angiogenic and that Ang2 may antagonize Ang1. Their studies were confined to the expression patterns of Ang1 and Ang2 in mouse embryos and adults; they also performed overexpression studies of Ang2. While they suggest that simultaneous regulation of VEGF and angiopoietins may positively promote revascularization or negatively prevent tumor growth, in no instance do they suggest that the combination can reduce or treat restenosis or atherosclerosis, namely plaque formation, which is not tumor growth.

While Maisonpierre *et al.* may suggest opposing roles for Ang1 and Ang2 in vascularization, Asahara *et al.* conclude that neither Ang1 nor Ang2 alone induce neovascularization. In their mouse corneal neovascularization model, they determined that the combination of VEGF and Ang1 increases vascular density and that the combination of VEGF and Ang2 increases the extent and length of vasculature. They provide no data, teachings or suggestions on the combination of a VEGF inhibitor and angiopoietin. Furthermore, the findings of Asahara

relate neither to restenosis nor to atherosclerosis, and teach nothing in regards to whether inhibitors of these molecules reduce vascularization, or reduce restenosis and/or atherosclerosis.

Further, it is unclear how the skilled artisan could expect a reduction in pathological angiogenesis from either Ang1 or Ang2 alone or in combination with another molecule from the teachings of the cited documents. Alone, they had no effect on neovascularization, and in combination with VEGF, both increased vascularization, albeit in different ways. Even considering the state of the art at the time the instant application was filed, it is not obvious that the combination of Ang1 and a VEGF inhibitor would reduce or treat restenosis or atherosclerosis.

Not only do the cited references, alone or in combination, neither teach nor suggest reduction or treatment of restenosis or atherosclerosis using a VEGF inhibitor and an inducer of vessel maturation, they also do not even contain concurring results. If the references cannot agree on the function of the molecules in question, the use of said molecules in treating disease cannot be obvious. Simply, the cited documents lack the necessary incentive or motivation for modifying their teachings to arrive at the instant invention. Further, they fail to provide the necessary suggestion of the desirability of the modification of the teachings, especially as "obvious to try" is not the standard under Section 103, and both the suggestion of an invention and the expectation of its success must be found in the prior art for a proper Section 103 rejection. *See In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993); *In re Fine,* 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988); *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992); *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

When combined, the teachings of these documents lead to the conclusion that VEGF is present in the macrophages that accumulate at the site of atherosclerotic plaques and which are partially responsible for the development of such plaques; that a VEGF inhibitor can inhibit tumor mitogenesis; that Ang2 is a natural antagonist of Ang1, and that the two play opposing roles in neovascularization, which contradicts further findings that neither Ang1 nor Ang2 alone induce neovascularization, rather, VEGF and Ang1 increase vascular density, and VEGF and Ang2 increase the extent and length of vasculature. The combination of such teachings would lead one of skill in the art to the conclusion that the current teachings are too diversified and contradictory to provide any expectation of success in providing a treatment for inhibiting tumor growth or corneal vascularization, let alone treatments for conditions which may or may not be related, including atherosclerosis and restenosis.

In fact, although atherosclerosis may be mentioned in Kendall's laundry list of possible uses for VEGF inhibitors (of which no evidence is provided that VEGF would be a suitable treatment for the majority of conditions listed, including atherosclerosis), atherosclerosis is not the focus of Maisonpierre or Asahara, neither of which even mention atherosclerosis or suggest that there may be similarities between the researched subject and atherosclerosis. Furthermore, restenosis was not considered or mentioned in any of the cited documents. Therefore, there would be no motivation to combine the teachings of the cited documents to arrive at a treatment for restenosis, such that new claims 18-25 relating to methods of treating or reducing restenosis should be allowed.

In sum, the cited references cannot be logically combined since their teachings with respect to the roles of Ang1 and Ang2 do not concur. The combination of the cited documents fails to teach or suggest the administration of VEGF and Ang1 to reduce or treat restenosis and/or atherosclerosis. Rather, the combination of the cited documents leads away from the instant invention because, reading the documents in combination in a light most favorable to the Examiner (without any admission, prejudice, estoppel or the like), the combination of the cited documents may direct the skilled artisan toward the administration of VEGF and Ang1 to promote vascularization or the administration of VEGF and Ang2 to inhibit tumor growth. However, promoting vascularization is contrary to treating restenosis and/or atherosclerosis, as these conditions are not tumors. Thus, what may be suggested by the combination of the cited references is not the instant invention, and in fact, leads away from it. The alleged modification of the documents cited in the Section 103 rejection is untenable in light of the full teachings of the cited documents; and, in view of the case law, the Section 103 rejection cannot stand. Therefore, reconsideration and withdrawal of the Section 103 rejection are requested.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance, or at least in better condition for appeal. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date.

Respectfully submitted,

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